A mechanistic investigation of ACE inhibitor dose effects on aerobic exercise capacity in heart failure patients

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Background Angiotensin converting enzyme inhibitors at high doses have been shown to improve prognosis of heart failure patients. Their beneficial effects on exercise capacity have been less convincing in large parallel group studies. The objective of this investigation was to explore the mechanisms involved in dose-related functional effects and to test the hypothesis that a trial recommended high dose of lisinopril would improve aerobic exercise capacity and cardiovascular function more than with a low dose.

Methods Twelve patients with symptomatic heart failure completed a randomized double-blind crossover trial of lisinopril 5 mg o.d. and 20 mg o.d. for 24 weeks, crossing over the doses at 12 weeks. The primary end-point was aerobic exercise capacity, and the secondary end-points were cardiac performance at peak exercise and dobutamine stimulation.

Results The aerobic exercise capacity (primary end-point) was significantly higher during the 5 mg per day dosage compared to the 20 mg (1696 vs 1578 ml min⁻¹, P=0·016), equivalent to a rise of 1·53 ml kg⁻¹ min⁻¹ from the 19·6 ml kg⁻¹ min⁻¹ with 20 mg when normalized by body weight. Seventy-three percent of patients showed greater peak oxygen consumption and peak cardiac power output with the 5 mg per day dose than the 20 mg, and none showed the opposite. In terms of cardiac performance, although the results were not statistically significant, there was a consistent pattern showing the same directional changes in favour of the lower dose in peak exercise cardiac power output and cardiac power output at maximal dobutamine. There were no significant differences in the resting values. A total of 24 adverse reactions were reported during the 5 mg phase compared to 38 during the 20 mg phase.

Conclusions Contrary to expectation, the aerobic exercise capacity of patients was found to be greater with the lower dose of lisinopril, suggesting that therapy with ACE inhibitors for heart failure may require tailoring the doses to the individual to optimize functional benefits in relation to the assumed prognostic benefits.

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Introduction

Improving quality and quantity of life are two complementary treatment objectives in heart failure. There is no doubt that ACE inhibitors improve the longevity of patients with heart failure1–3. However, their effects on one major determinant of quality of life, the exercise capacity, are not so clear4–7. One of the most perplexing finding is that ACE inhibitors with proven mortality benefits, such as enalapril1,2,8, ramipril9 and trandolapril10, have been shown in large-scale studies not to improve the exercise capacity of patients with heart failure6,11,12. There is a general belief that the higher the dose of ACE inhibition (e.g. lisinopril >30 mg per day),
the greater the benefit, despite the fact that there was no significant difference in mortality rates between the high and low doses in the ATLAS study.\[13\].

In a recent review article\[14\], we demonstrated that the belief in a monotonic rise in exercise capacity directly proportional to the extent of vasodilatation may not be consistent with fundamental principles of cardiovascular physiology. Briefly, at excessively high doses of any vasodilator, even normal healthy subjects will feel syncopeal and therefore unable to exercise well. At the other end of the spectrum, if vasoconstriction is excessive, then cardiac output is compromised, thereby limiting exercise ability. Somewhere between these extremes, there is an optimum vasodilatory state when the subject can perform the most exercise. With excessive circulating noradrenaline\[15\] as in heart failure\[16\] when other vasoconstrictive mechanisms are also activated\[17\], the operating point is shifted to higher levels of systemic vascular resistances than at the optimal point, resulting in suboptimal cardiac power output and reduced aerobic exercise capacity. Thus, the already weakened heart has to pump against a greater resistance than is optimal. Vasodilatory therapy would remedy this situation, but if too high a dose of vasodilator is given, overvasodilatation occurs, and the operating point becomes shifted beyond the optimal point (Fig. 1).

This investigation is chiefly to explore what mechanisms are operative when ACE inhibitors affect the cardiovascular function and exercise capacity in heart failure patients. The hypothesis to be tested can be expressed in a falsifiable form: that chronic therapy with a trial recommended dose of ACE inhibitor, such as lisinopril 20 mg per day, would produce vasodilatation and greater aerobic exercise capacity than with a lower dose (e.g. 5 mg per day), through maximizing peak cardiac power output. Such an effect is depicted in Fig. 1, with the 20 mg vasodilatation shifting the operating point to B or C, and the corresponding 5 mg per day shifts it to A and B (both suboptimal). Optimum vasodilatation would shift the operating point to C. If this were achieved by 20 mg, then 5 mg would produce suboptimal results (points A or B); and vice versa if the optimum is achieved by 5 mg (with 20 mg to point D).

**Figure 1** Haemodynamic effects of vasodilatation as illustrated in terms of pump-load (cardiac-pump/vascular) interactions. In the graph, the cardiac power output or work is zero when the systemic vascular resistance is at either end of the spectrum: zero or infinite. At optimal vascular resistance, the cardiac power output is maximal. This is the usual operating point of a normal subject. In heart failure, the operating point is shifted to higher vascular resistances and arterial vasodilatation would shift the operating point to either side of the optimum. In individual heart failure patients, it was hypothesized that lisinopril 20 mg per day would produce vasodilatory shift of the operating point to points marked by B and C, while the corresponding 5 mg per day shifts it to A and B (both suboptimal). Optimum vasodilatation would shift the operating point to C. If this were achieved by 20 mg, then 5 mg would produce suboptimal results (points A or B); and vice versa if the optimum is achieved by 5 mg (with 20 mg to point D).
exercise end-points because of potential mismatching of groups when there are dropouts. This investigation was therefore conducted as a crossover trial.

**Methods**

**Study design, patients, outcome measures**

This randomized, double-blind, crossover study was designed to compare the effects of a high dose (20 mg o.d.) and a low dose (5 mg o.d.) of lisinopril on exercise capacity, cardiac reserve and vasodilatation in patients with congestive heart failure. The primary end-point was aerobic exercise capacity (peak oxygen consumption) during incremental exercise testing, and the secondary end-points were cardiac reserve at peak exercise and dobutamine stimulation.

Ambulatory patients with known congestive cardiac failure (NYHA class II–III) were recruited from the outpatient clinic. All patients had a left ventricular ejection fraction (measured using standard echocardiographic techniques) of less than 45% and had been treated with diuretics, with or without digoxin and ACE inhibitors for >60 consecutive days before entering the study. The aetiology of heart failure were coronary artery disease, chronic hypertension or idiopathic dilated cardiomyopathy. Each subject was able to perform exercise for at least 4 min using the modified Bruce protocol, with heart failure symptoms as the end-point of exercise (e.g. fatigue, exhaustion, dyspnoea) and not other symptoms such as angina, claudication or musculoskeletal pains, and achieve a respiratory exchange ratio of >1.0. The study protocol was approved by the local ethics committee. Informed consent was obtained in all cases.

After a 4-week single-blind placebo run-in period, eligible patients were randomized to receive either lisinopril 5 mg or lisinopril 20 mg for 12 weeks (Period 1). After the 12 weeks, patients crossed over, without a washout period, to receive the treatment dose alternative to the one received during Period 1, for a further 12 weeks (Period 2).

Exercise tests were performed on entry, after the 4 weeks of placebo run-in and at the end of each 12-week treatment period, about 2–6 h post ingestion of medication. Dobutamine stress tests were performed after 2 weeks of placebo run-in and at the end of each 12-week treatment period 1 week before the exercise tests. These tests were performed on average 4 h after the patients had taken the lisinopril medication. Clinical assessments, blood testing and monitoring for adverse events were performed at regular intervals during the study.

**Cardiopulmonary exercise tests**

These were conducted as described in a previous report[18]. A symptom-limited exercise test was performed using the modified Bruce protocol to measure the peak VO₂, peak VCO₂, anaerobic threshold, respiratory exchange ratio, maximum heart rate and exercise duration, using MedGraphics CardiO₂ equipment (Medical Graphics Corporation, St Paul, U.S.A.). A second peak single-stage exercise test, set at approximately the peak workload attained during the incremental test, was then performed for long enough to allow at least two measurements of peak cardiac output (indirect Fick method using carbon dioxide re-breathing techniques) and peak cardiac power output calculated therefrom. The cardiac power output was calculated from the mean cardiac output and mean arterial pressure[19].

**Dobutamine stress tests**

Dobutamine was infused via a peripheral vein at an initial dose of 10 μg·kg⁻¹·min⁻¹, increasing in steps of 10 μg·kg⁻¹·min⁻¹ at intervals of 10 min. The cardiac output, blood pressure and 12-lead ECG were recorded at the end of each stage. The dobutamine was increased until no further increase in cardiac output occurred or the dose of 40 μg·kg⁻¹·min⁻¹ was reached, unless the subject had limiting symptoms at a lower dose.

The cardiac outputs and blood pressure measurements were determined at rest and during increasing doses of dobutamine. The stroke distance was measured by Doppler ultrasound and multiplied by the heart rate and aortic root area to obtain the cardiac output. A 2 MHz Doppler probe (Doptek Decoder 25, Doptek Ltd, Chichester, U.K.) was placed in the subject’s suprasternal notch. The stroke distance was measured by the calculated intensity weighted mean frequency of each aortic Doppler pulse. The stroke distance was obtained for at least 10 consecutive cardiac cycles. The mean stroke distance was then calculated.

The aortic cross-sectional area was estimated from the cardiac output measured by the carbon dioxide rebreathing method. Simultaneous Doppler stroke distance and carbon dioxide rebreathing cardiac output measurements were made at rest. The aortic cross-sectional area was calculated as the cardiac output divided by the product of the stroke distance and the heart rate. This aortic cross-sectional area was then used to calculate the cardiac output from the Doppler stroke distance during the incremental dobutamine infusion.

**Statistical analysis**

Between-treatment comparisons were performed using the analysis of variance methods appropriate to the two-period crossover design, as outlined by Grizzle[20]. Baseline values were incorporated into the analysis, as recommended by Armitage and Hills[21]. Means adjusted for period effects are presented for each of the two dose levels, together with the difference between adjusted means and the corresponding 95% confidence interval for the difference. A P-value of ≤0.05 was taken to represent statistical significance.
Results

Clinical features

Nineteen patients were recruited to participate in this pilot study and randomized to treatment phases. The mean age was 62.9 years (range 55–76). The mean left ventricular ejection fraction was 37.4% (range 18–44%). The majority of the patients had ischaemic heart disease (53%) and dilated cardiomyopathy (31%) as the aetiology. The patients were in either NYHA functional class II (79%) or III (21%). The baseline characteristics of the patients who entered the study are shown in Table 1. Five patients withdrew during the 20 mg phase (two due to cough, one headaches, one diarrhoea, one non-compliance), and during the 5 mg phase one withdrew (due to MI) and one died (pancreatitis). Twelve patients completed the crossover study and only their complete set of data were entered into the final analyses for hypothesis testing.

During the 5 mg treatment phase 11 patients reported a total of 24 adverse events, whereas 16 patients reported 38 adverse events during the 20 mg treatment phase. The most commonly reported events on lisinopril 5 mg were dizziness, dyspnoea and pharyngitis, and the most commonly reported events on lisinopril 20 mg were dizziness, asthenia and headache. There was a tendency towards higher levels of serum urea (8.31 vs 6.85 mmol l⁻¹) and creatinine (119.3 vs 106.1 μmol l⁻¹) with the 20 mg dose than with the 5 mg dose, although the differences were not statistically significant.

Vasodilatory effects of ACE inhibition

There were no statistically significant differences in the resting baseline central haemodynamics as shown in the mean values adjusted for period effect in Table 2. As shown in Fig. 2(a) and (b), there were monotonic dose

Table 1 Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>18 (95%)</td>
</tr>
<tr>
<td>Age</td>
<td>62.9 years (range 55–76)</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>37.4% (range 18–44%)</td>
</tr>
<tr>
<td>Aetiology</td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>10 (53%)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>6 (31%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
</tr>
<tr>
<td>NYHA II</td>
<td>15 (79%)</td>
</tr>
<tr>
<td>NYHA III</td>
<td>4 (21%)</td>
</tr>
<tr>
<td>Mean daily dose of frusemide</td>
<td>67.3 mg (range 40–80)</td>
</tr>
</tbody>
</table>

Table 2 Treatment effects of high vs low dose

<table>
<thead>
<tr>
<th>Variables</th>
<th>Lisinopril 5 mg o.d.‡</th>
<th>Lisinopril 20 mg o.d.‡</th>
<th>A (5 mg–20 mg)</th>
<th>95% CI for A</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO₂rest (ml min⁻¹)</td>
<td>340.5 ± 362.3</td>
<td>-21.8 ± 360.3</td>
<td>-94.5 to 50.8</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>VO₂rest/kg</td>
<td>4.25 ± 4.51</td>
<td>-0.06 ± 4.2</td>
<td>-1.10 to 0.58</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>116.2 ± 108.9</td>
<td>7.3 ± 105.2</td>
<td>-6.9 to 21.4</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72.0 ± 66.1</td>
<td>5.9 ± 64.2</td>
<td>-1.7 to 13.5</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>83.8 ± 81.2</td>
<td>6.4 ± 80.0</td>
<td>-2.6 to 15.4</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td>HR (beats min⁻¹)</td>
<td>79.0 ± 85.0</td>
<td>-6.0 ± 83.8</td>
<td>-15.3 to 3.3</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>COrest (l min⁻¹)</td>
<td>5.6 ± 5.8</td>
<td>-0.17 ± 5.6</td>
<td>-14.0 to 0.7</td>
<td>0.67</td>
<td></td>
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<tr>
<td>CPORest (watts)</td>
<td>0.97 ± 0.91</td>
<td>-0.06 ± 0.91</td>
<td>-0.09 to 0.21</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>Urea (mmol l⁻¹)</td>
<td>7.4 ± 8.1</td>
<td>-0.6 ± 7.4</td>
<td>-3.5 to 2.3</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Creat (mg/dl)</td>
<td>111 ± 120</td>
<td>-9.8 ± 112</td>
<td>-38.3 to 18.7</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO₂peak (ml min⁻¹)</td>
<td>1696 ± 1578</td>
<td>117.6 ± 1564</td>
<td>26.5 to 208.7</td>
<td>0.016*</td>
<td></td>
</tr>
<tr>
<td>VO₂peak/kg</td>
<td>21.2 ± 19.6</td>
<td>1.53 ± 21.4</td>
<td>0.42 to 2.65</td>
<td>0.012*</td>
<td></td>
</tr>
<tr>
<td>Ex Dur (min)</td>
<td>12.47 ± 11.84</td>
<td>0.63 ± 11.7</td>
<td>-0.66 to 1.91</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>RER</td>
<td>1.03 ± 1.07</td>
<td>-0.04 ± 1.05</td>
<td>-0.11 to 0.04</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>HRpeak (beats min⁻¹)</td>
<td>139 ± 134</td>
<td>4.7 ± 133</td>
<td>-1.2 to 10.7</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>COpeak (l min⁻¹)</td>
<td>12.2 ± 11.9</td>
<td>0.31 ± 11.8</td>
<td>-0.10 to 0.71</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>CPoppeak (watts)</td>
<td>2.74 ± 2.63</td>
<td>0.11 ± 2.61</td>
<td>-0.08 to 0.29</td>
<td>0.24</td>
<td></td>
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</tbody>
</table>

‡Mean adjusted for period effect.

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Figure 2  Effects of lisinopril 5 mg and 20 mg per day, compared to those during the baseline placebo run-in phase, on (a) systemic mean arterial pressure (MAP) and, (b) systemic vascular resistance (SVR), showing incremental vasodilation with higher doses; on (c) peak oxygen consumption (VO$_2$max), the pre-assigned primary end-point, and (d) exercise duration during symptom-limited exercise testing; on peak cardiac power output (CPO$_{max}$) during (e) symptom-limited treadmill exercise testing, and (f) during incremental intravenous dobutamine infusions.
related vasodilatory effects of lisinopril, with the 20 mg per day dose producing greater reduction in systemic arterial pressure and systemic vascular resistance than the 5 mg per day dose and the placebo during the baseline run-in phase.

**Primary end-point: aerobic exercise capacity**

Despite the monotonic dose-related decreases in systemic vascular resistance, the responses in exercise capacity demonstrated a different pattern. As shown in Fig. 2(c), the aerobic exercise capacity was significantly greater with the 5 mg per day dose of lisinopril, compared to the placebo and the 20 mg per day dosage. The same pattern was found when the less precise exercise duration was used as an indicator of exercise capacity (Fig. 2(d)). Comparing the double-blinded periods only and formally adjusting for period effects, the primary end-point of peak exercise oxygen consumption was found to be significantly greater during the lisinopril 5 mg phase than during the lisinopril 20 mg o.d. phase (1696 ml . s\(^{-1}\) vs 1578 ml . s\(^{-1}\), \(P=0.016\)). The majority of patients had higher aerobic exercise capacity during the 5 mg dose than the 20 mg dose. The difference between the \(\Delta VO_2\text{max}\) was 118 ml . s\(^{-1}\) and the 95% confidence interval for the difference was between 27 and 209 ml . s\(^{-1}\). When the oxygen consumption was normalized for body weight, this difference was still statistically significant (21·17 vs 19·63 ml . kg\(^{-1}\) min\(^{-1}\), \(P=0.012\), difference: 1·53 ml . kg\(^{-1}\) min\(^{-1}\), 95% CI 0·42 to 2·65). There was a tendency towards greater exercise test duration during the 5 mg lisinopril treatment phase (12·47 vs 11·84 min, difference: 0·63 min, 95% CI −0·66 to 1·91). All patients exercised beyond respiratory exchange ratio >1·0, implying that they all exercised consistently to cardiopulmonary limits expected of patients in heart failure.

**Stress haemodynamics and exercise capacity**

Similar in pattern to exercise capacity in relation to lisinopril doses, we found that the highest cardiac power output during maximal exercise and dobutamine challenge occurred with the 5 mg per day dosing, as compared to during the placebo run-in or with the 20 mg dosing (Fig. 2(e) and (f), although the differences did not reach statistical significance. Comparing the double-blinded periods only and formally adjusting for period and carry over effects, the peak cardiac power output during maximal exercise was found to be greater during the lisinopril 5 mg phase than during the lisinopril 20 mg o.d. phase (2·74 vs 2·63 W, \(P=0·19\)) during the 5 mg phase compared to the 20 mg phase and placebo (Fig. 2(f)).

When the changes in cardiac power output and oxygen consumption are plotted on the same graph in Fig. 3, it is apparent that the majority of patients (73%)
showed greater aerobic exercise capacity and cardiac pumping capability with the 5 mg dose than with 20 mg per day. None of the patients showed a greater peak oxygen consumption and peak cardiac power output with the 20 mg dose than with the 5 mg.

Discussion

Whilst the benefit of ACE inhibitors in terms of prognosis is well established\(^1\) data on their effects with regard to exercise capacity are rather conflicting\(^7,14,22\). This investigation was undertaken to explore the mechanisms whereby ACE inhibitors affect cardiovascular function at rest and during maximal exercise and inotropic stimulation in order to throw some light as to why there are confusing data. Not surprisingly, we found that exercise capacity (the pre-determined primary end-point) when they were taking the lower dose lisinopril (5 mg per day) than the higher dose (20 mg per day, Fig. 2(c)). The magnitude of difference in peak oxygen consumption between the 5 and 20 mg of lisinopril was 1.53 ml kg\(^{-1}\) min\(^{-1}\), which should not be taken to be trivial when considering that in controlled trials of exercise training in heart failure patients, the average gain is 2.87 ml kg\(^{-1}\) min\(^{-1}\) (range: 0–1 to 5.8 ml kg\(^{-1}\) min\(^{-1}\))\(^23\).

This experimental finding therefore contradicts the notion that exercise capacity increases monotonically with increasing doses of ACE inhibitors without any apparent upper limits of dose. The results also do not support our proposed hypothesis that the 20 mg per day of lisinopril was more likely than 5 mg to enable the failing hearts to function at an optimal vasodilatory state (Fig. 1) in order to produce enhanced cardiac power output and oxygen consumption during peak exercise. It would appear that in our cohort of heart failure patients, the lower dose of 5 mg per day was more likely to produce the optimal vasodilatation (point C in Fig. 1) for enhancing aerobic exercise capacity. The pattern of responses shown in Fig. 2 indicated that there was also a consistent tendency to greater exercise duration, higher peak cardiac power output during maximal exercise and during maximal dobutamine stimulation, further suggesting that the 5 mg per day dose was associated with greater enhancement of cardiovascular function. In cardiac failure, we and others have previously demonstrated that peak cardiac power output is a major determinant of exercise capacity\(^18,24,25\) and prognosis\(^19,26–28\). It would appear from this study that cardiac power output considerations, especially in terms of impedance matching\(^14\), is also helpful in understanding the dynamics of how vasodilators affect functional capacity.

In a complementary study with a patient population and crossover study design similar to the present study, but investigating the neurohumoral effects of 20 mg o.d. vs 5 mg o.d. of lisinopril, Davison et al\(^29\) showed that the systolic and diastolic blood pressure were lower by a mean of 3–6 mmHg over the 24 h with the 20 mg dose, indicating greater vasodilatation, similar to our observation (Table 2 and Fig. 2(a)). This was associated with lower plasma aldosterone levels over the entire 24 h, but there was no observable difference between plasma ANP or BNP levels throughout the 24 h\(^30\). It would appear that from the neurohormonal modulatory point of view, the high doses (30–35 mg o.d.) of lisinopril found in the ATLAS Study were beneficial prognostically, mainly in terms of reducing hospitalization rates\(^13\), but this was not supported by the smaller NETWORK Study\(^31\).

Neither of these studies investigated the impact of differing doses on exercise capacity or cardiovascular function.

ACE inhibition and exercise capacity

When reviewing all published studies on the effects of ACE inhibitors on exercise capacity, Swedberg and Gundersen\(^7\) found that there was no consistent evidence that ACE inhibitors improved the exercise capacity of patients with heart failure. One of the problems in these studies is that symptom-limited exercise tests are highly dependent on the reliability of the patients’ subjective perception of their symptoms and willingness to exercise to true limits. To ensure reliability of the collected exercise data, we use breath-by-breath monitoring of respiratory gases, which allows better guidance on objective exercise end-points.

The concept of monotonically greater exercise capacity directly proportional to higher doses of ACE inhibitors has been reinforced by studies by Riegger\(^32,33\), van Veldhuisen and colleagues\(^34\) and Brunner-La Rocca and colleagues\(^35\), who reported greater exercise capacity with higher doses of ACE inhibitors without an apparent maximum of dose being reached in the studies. However, it is important to note that the exercise tests in these studies were conducted at the trough drug levels, i.e. just before the next scheduled dose administration. This is quite different from other studies that conducted exercise tests a few hours post dosing during high plasma drug levels. At these trough drug levels, the extent of vasodilatation produced by the high doses may be equivalent to that produced a few hours after ingestion of lower doses, such as a few hours post 5 mg dosing in our study. Therefore, a key issue in the interpretation of trial results is not just the doses used, but also when the exercise tests were conducted after drug ingestion.

Two parallel-group randomized double blind controlled studies\(^36,37\) comparing different doses of ACE inhibitors and a non-randomized fortnightly dose-escalation study\(^38\) showed no significant dose-related differences in peak oxygen consumption. A large proportion of patients dropped out of the latter study (45% of total), similar to the 48% in Pacher’s study\(^37\) and the
37% in our study. The problem of dropouts significantly affects the interpretation of the results of parallel group studies but not that of crossover trials. Removing dropouts from analyses disturbs the original comparability (through randomization) of the parallel treatment groups thereby unbalancing the groups. The resulting observed differences might turn out to be due to the imbalance (equivalent to selection bias) of patient cohorts rather than true differences in treatment effects. A parallel group study design is considered to be preferable for mortality studies, but has severe limitations when investigating drug effects on exercise capacity, quality of life and cardiovascular performance, mainly because values for dropouts have to be arbitrarily assigned. Because of this, we had elected to adopt a crossover design as the patients acted as their own controls. This methodology allows detection of smaller differences without having to recruit enormously large numbers of patients. Hence, our small exploratory study was able to produce a significant and reliable difference in the primary end-point.

**Study limitations**

One limitation of the present study is that only two doses (5 mg and 20 mg o.d.) of lisinopril were tested. To test more doses would require an acute study or shorter durations of follow-up, although acute or short-term responses to ACE inhibition may not reflect patient response during chronic therapy. A 3-month period of treatment is considered to be a minimum for patients to reach a steady state of chronic therapy. To test more doses in a chronic therapeutic trial of this nature is impracticable as the study period for each participant would be too long, and the number of tests performed on each patient would be too high to expect full compliance. Since this study is the first of its kind to test such a hypothesis we have elected to test a dose that is commonly used in routine clinical practice (5 mg o.d.), and a higher dose recommended according to clinical mortality trials of ACE inhibitors (20 mg o.d. of lisinopril).

**Implications and conclusions**

In each individual heart failure patient, depending on the severity of heart failure and the extent of compensatory vasoconstriction, there is a point of vasoconstriction at which the heart and the vascular system match optimally. Heart failure patients with a greater tendency to vasoconstriction would presumably require higher doses of ACE inhibition (20–40 mg of lisinopril o.d.) to reach the pump-load matchpoint. Hypotensive patients can usually tolerate only lower doses of ACE inhibitors. The results of this study therefore provide a wider perspective for prescribing ACE inhibitors to heart failure patients. Against the backdrop of potential prognostic benefits that can only be assumed for the individual patients (since the trial results on improved prognosis can only be taken by faith to be applicable to the individual patient, and cannot be proven or demonstrated unlike improvements in symptoms and exercise tolerance), we believe that treatment approaches should now shift from unthinking escalation of doses of ACE inhibitors to a pre-set high dose to tailoring treatment according to the individual patient’s particular objectives.

The unexpected results from this pilot study suggest that a large multicentre crossover controlled trial looking into the effects of high vs low doses of ACE inhibitors should be considered and conducted in the most prevalent age-group of the heart failure population, the elderly, to investigate the impact on their exercise capacity and on other aspects of quality of life.

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